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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/854,356	05/09/2001	Martin A. Cheever	014058-009811US	1297

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EXAMINER	
BRISTOL, LYNN ANNE	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 08/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/854,356	CHEEVER ET AL.	
	Examiner	Art Unit	
	Lynn Bristol	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *113,114,116-125 and 145-154* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *113,114,116-125 and 145-154* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/23/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

2. The amendment filed on May 23, 2006, is considered non-compliant because it fails to meet the requirements of 37 CFR § 1.121, as amended on June 30, 2003 (see *68 Fed. Reg. 38611*, Jun. 30, 2003). However, in order to advance prosecution, rather than mailing a Notice of Non-Compliant Amendment, Applicant is advised to correct the following deficiency in replying to this Office action: The amendment is non-compliant because the status identifier in parentheses of claim 116 that has been currently amended does not properly indicate that status.

3. Amended Claims 113 and 116 and new claims 145-154 find support in the original specification as filed and have been entered.

4. Applicants explanation on p. 4, ¶5 of the response that the Her-2/neu fusion protein of SEQ ID NO: 7 comprises the extracellular domain and a portion of the phosphorylation domain (Delta PD fragment) of the full length Her-2/neu protein is acknowledged.

5. Claims 113, 114, 116-125 and 145-154 are all the pending claims and all the claims under examination.

The text of those sections of Title 35, US Code not included in this action can be found in a prior Office Action.

Information Disclosure Statement

6. The US patents, the US patent publication, international patent applications and the nonpatent literature references have been considered and entered.

Rejection of Priority Claim-Withdrawn

7. The Examiners rejection of Applicants assertion that Claims 113, 114 and 117-125 obtain benefit to the priority dates for Application Nos. 09/493,480 and 60/117,976 for the limitation "at least 90% identity to SEQ ID NO:6", has been withdrawn in view of Applicants comments (p. 4, ¶8- p. 5, ¶1) and the amendment of the claims to delete the limitation.

Withdrawal of Rejections

8. The rejection of Claims 113, 114 and 117-125 under 35 USC §112, first paragraph, is withdrawn in view of Applicants comments (p. 4, ¶7) and the amended claims to delete the recitation for "at least 90% identity to SEQ ID NO:6".

102 Rejection- Maintained

9. The rejection of Claims 113, 114, 116, 118, 119, 121, 145-148 and 150 under "35 USC 102(b)" [Examiner's correction to 102(e)] as being anticipated by Cheever et al.

(USPN 5,869, 445; published February 9, 1999; filed April 1, 1996; hereinafter referred to as "Cheever") is maintained. Applicants comment on p. 5, ¶2 that the amendments to claim 113 have obviated the rejection are not found persuasive. In view of the amendments of Claim 116, Cheever now reads on the claim and the dependent claims thereof.

The interpretation of Claims 113, 114, 118, 119, and 121 was discussed in the previous office action. Claims 116, 145-148 and 150 are drawn to a method for eliciting or enhancing an immune response in warm-blooded animal comprising administering a composition comprising an isolated protein comprising a HER-2/neu fusion protein comprising amino acid sequence comprising SEQ ID:7, wherein the Her-2/neu fusion protein produces the immune response, the composition comprising a vaccine, the fusion protein being lipidated, and the composition further comprising a carrier such as water-in-oil emulsion and/or an immunostimulatory substance.

Cheever discloses methods for eliciting or enhancing an immune response using an isolated protein comprising a HER-2/neu fusion protein comprising SEQ ID NO: 6 or 7 (trxA-human HER-2/neu polypeptide; Example 1); polypeptides including variants of the polypeptide of SEQ ID NO:2 from amino acid 676 through amino acid 1255, that retain the ability to stimulate an immune response (Col. 5, lines 58-62); use of the her-2/neu proteins to elicit or enhance an effective autochthonous immune response to convert a HER-2/neu positive tumor to HER-2/neu negative (Col. 4, lines 47-50); a polypeptide based on a particular portion (HER-2/neu polypeptide) of the protein expression product of the HER-2/neu gene can be recognized by thymus-dependent

lymphocytes (hereinafter "T cells") and, therefore, the autochthoncus immune T cell response can be utilized prophylactically or to treat malignancies in which such a protein is or has been overexpressed (Col. 4, lines 53-58); using the polypeptides to treat malignancies include breast, ovarian, colon, lung and prostate cancers (Col. 14, lines 22-29); eliciting or enhancing T cells (Col. 14, line 34-46; Col. 15, lines 8-14) and inducing B cells to produce antibodies (Col. 17, lines 10-16); lipidated forms of the polypeptide (Col. 6, line 6); immunization with a HER-2/neu peptide (i.e., as a vaccine) as a pharmaceutical composition in combination with a pharmaceutically acceptable carrier, excipient or diluent and carriers comprising water-in-oil emulsions, and compositions further comprising immunostimulatory substances (Col. 15, lines 39-44, 48-55).

Applicant is reminded that because the claims recite "comprising" language, any fusion polypeptide comprising an amino acid sequence comprising SEQ ID NO:6 or 7 is encompassed by the claims, and therefore anticipated by Cheever.

103 Rejections- Maintained

10. The rejection of Claims 113 and 117 under 35 USC 103(a) as being unpatentable over Cheever et al. (USPN 5,869,445; published February 9, 1999; filed April 1, 1996; hereinafter referred to as "Cheever") in view of Forsgren (WO91/18926; published December 12, 1991; filed February 21, 1991); hereinafter referred to "Forsgren") is maintained. Applicants comment on p. 5, ¶3 that the amendments to claim 113 have obviated the rejection are not found persuasive. See the Examiner's new comments with respect to Cheever as discussed under section 9, supra. Applicant is reminded that

because the claims recite "comprising" language, any fusion polypeptide comprising an amino acid sequence comprising SEQ ID NO:6 is encompassed by the claims, and therefore obvious over Cheever in view of Forsgren.

11. The rejection of Claims 113, 116, 119, 120, 122, 123, 124 and 149 and 151-153 under 35 USC 103(a) as being unpatentable over Cheever et al. (USPN 5,869, 445; published February 9, 1999; filed April 1, 1996; hereinafter referred to as "Cheever") in view of Garcon (WO95/17210; filed July 2, 1996; hereinafter referred to as "Garcon") is maintained. Applicants comment on p. 5, ¶3 that the amendments to claim 113 have obviated the rejection are not found persuasive. In view of the amendments of Claim 116, the claim and its dependent claims are rendered obvious over Cheever in view of Garcon.

The interpretation of Claims 113, 119, 120, 122, 123, and 124 was discussed in the previous office action. The interpretation of Claim 116 is discussed supra. Claims 149 and 151-153 are drawn to the composition comprising tocopherol, an immunostimulatory substance such as 3D-MPL or QS21, 3D-MPL or QS21 or the combination in an oil-in-water emulsion, or 3D-MPL or QS21 or the combination and tocopherol in an oil-in-water emulsion.

The interpretation of Cheever was discussed supra. Cheever does not disclose composition comprising tocopherol, an immunostimulatory substance such as such as 3D-MPL or QS21, 3D-MPL or QS21 or the combination in an oil-in-water emulsion, or 3D-MPL or QS21 or the combination and tocopherol in an oil-in-water emulsion. Garcon rectifies this deficiency in its disclosure.

Garcon discloses tocopherol or 3D-MPL, QS21 or the combination in an oil-in-water emulsion, are well known adjuvants [0002, 0003]; combining tocopherol, 3D-MPL, and QS21 with an antigen improves vaccine formulations [0011].

It would have been *prima facie* obvious to have produced the instantly claimed immune response eliciting or enhancing methods in view of Cheever and Garcon.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced the instant claimed methods in view of Cheever and Garcon because Cheever discloses that it is desirable to include other components in the vaccine, such as a vehicle for antigen delivery and immunostimulatory substances designed to enhance the protein's immunogenicity (Col. 15, lines 48-52) and because Garcon discloses that "in general, preformed soluble antigen does not reach the processing and presentation pathway, and do not elicit class I restricted CTL. Therefore conventional non-living vaccines, while eliciting antibody and T helper responses, do not generally induce CTL mediated immunity. The combination of the two adjuvants QS21 and 3D-MPL together with an oil-in-water emulsion can overcome this serious limitation of vaccines based on recombinant proteins, and induce a wider spectrum of immune responses [0011]. One skilled in the art at the time of the invention would have had the reagents available to have produced a composition comprising the instant claimed elements according to Cheever and Garcon in order to use the composition in a method to obtain an improved, broad spectrum immune eliciting or enhancing response to a specific antigen.

Thus the claims were prima facie obvious at the time of the invention in view of Cheever and Garcon. Applicant is reminded that because the claims recite "comprising" language, any fusion polypeptide comprising an amino acid sequence comprising SEQ ID NO:6 or 7 is encompassed by the claims, and therefore obvious in view of Cheever and Garcon.

12. The rejection of Claims 113,116, 125 and 154 under 35 USC 103(a) as being unpatentable over Cheever et al. (US Patent 5,869, 445; published February 9, 1999; filed April 1, 1996; hereinafter referred to as "Cheever") in view of Krieg (WO 96/02555; filed July 15, 1994) is maintained. Applicants comment on p. 5, ¶3 that the amendments to claim 113 have obviated the rejection are not found persuasive. In view of the amendments to Claim 116, the claim and its dependent claim are rendered obvious over Cheever in view of Krieg.

The interpretation of Claims 113 and 125 was discussed in the previous Office Action. The interpretation of Claim 116 was discussed supra. Claim 154 is drawn to a composition comprising a CpG containing oligonucleotide.

The interpretation of Cheever is discussed supra. Cheever does not disclose a composition comprising a CpG containing oligonucleotide. Kreig recitifies this deficiency in its disclosure.

Kreig discloses using CpG oligonucleotides to stimulate a subject's response to a vaccine (Abstract).

It would have been *prima facie* obvious to have produced the instantly claimed immune response eliciting or enhancing methods in view of Cheever and Kreig.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced the instant claimed methods in view of Cheever and kreig because Cheever discloses that it is desirable to include other components in the vaccine, such as a vehicle for antigen delivery and immunostimulatory substances designed to enhance the protein's immunogenicity (Col. 15, lines 48-52) and because Kreig discloses that "the immunostimulatory oligonucleotides can be administered in conjunction with a vaccine as adjuvant to boost a subject's immune system to effect better response from the vaccine" (p. 21, lines 18-20). One skilled in the art at the time of the invention would have had the reagents available to have produced a composition comprising the instant claimed elements according to Cheever and Kreig in order to use the composition in a method to obtain an improved, broad spectrum immune eliciting or enhancing response to a specific antigen.

Thus the claims were prima facie obvious at the time of the invention in view of Cheever and Kreig. Applicant is reminded that because the claims recite "comprising" language, any fusion polypeptide comprising an amino acid sequence comprising SEQ ID NO:6 or 7 is encompassed by the claims, and therefore obvious in view of Cheever and Krieg.

Grounds for New Rejections

Applicant's amendments to the claims have necessitated new grounds for rejections.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 113 and 116 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claims 113 and 116 are indefinite for the recitation "capable of producing an immune response" as the term "capable" is not a positive limitation for the molecule actually possessing the claimed property of producing an immune response. The specification does not provide a definition for the term, thus the metes and bounds of the claimed invention cannot be determined.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 113-125 and 145-154 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of eliciting an immune response using a Her-2/neu fusion protein comprising SEQ ID NOS: 6 or 7 to stimulate T-cell proliferation and cytotoxicity and to induce B cells to produce an antibody, for use in treating malignancies such as breast, ovarian, colon, lung and prostate cancers, does

not reasonably provide enablement for using the method to elicit a specific immune response against just any disorder much less just any cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Claims 113-125 and 145-154 are drawn to a general method for eliciting or enhancing an immune response in warm-blooded animal comprising administering a composition comprising an isolated protein comprising a HER-2/neu fusion protein comprising an amino acid sequence comprising SEQ ID:6 (Claims 113, 114, 117-125) or SEQ ID NO:7 (Claims 116, 145-154), wherein the Her-2/neu fusion protein produces the immune response.

The specification teaches methods for inhibiting or preventing the development of a cancer in a patient by eliciting or enhancing and immune response to the HER-2/neu protein, comprising administering to a patient a pharmaceutical composition or vaccine as recited above. The patient may be afflicted with, e.g., breast, ovarian, colon, lung or prostate cancer [0012]; stimulating and/or expanding T cells specific for a HER-2/neu fusion protein [0014, 0070-0074]; stimulating B-cells to produce antibodies capable of recognizing HER-2/neu fusion proteins [0228]; and using the proteins in cancer therapy in general [0237-0245].

Claims 113-125 and 145-154 encompass eliciting or enhancing any kind of immune response and using the immune response in applications to treat any kind of disorder. The specification does not enable or support using the method of enhancing or eliciting the immune response for anything but treating breast, ovarian, colon, lung and

prostate cancers. There are no working examples in applicant's specification to guide the skilled artisan in practicing a method of eliciting or enhancing a specific immune response to treat any kind of tumor in a patient.

Furthermore, it would take one skilled in the art an undue amount of experimentation to determine what route of administration (*e.g.* intravenous, dermal, nasal, rectal, vaginal, inhalation, or topical administration) would result in a specific immune enhancing or eliciting response using the polypeptide comprising a Her-2/neu fusion protein comprising an amino acid sequence comprising SEQ ID NO: 6 or SEQ ID NO:7. The amount of direction or guidance presented in the specification is limited, and would not permit a person skilled in the art to use the invention without undue experimentation at the time the invention was made.

In view of the undue experimentation that would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for eliciting or enhancing a specific immune response in a subject where there is a practical endpoint for other than affecting breast, ovarian, colon, lung and prostate cancer, the enablement provided by the specification is not commensurate in scope with the claimed invention.

Claim Rejections - 35 USC § 102

15. Claims 113, 114, 116, 118, 145 and 147 are rejected under 35 U.S.C. 102(e) as being anticipated by Laus et al. (USPN 5976546; published November 2, 1999; priority filing date Dec. 28, 1995; hereinafter referred to as "Laus").

Claims 113, 114, 116, 118, 145 and 147 are drawn to a method for eliciting or enhancing an immune response in warm-blooded animal comprising administering a composition comprising an isolated protein comprising a HER-2/neu fusion protein comprising amino acid sequence comprising SEQ ID:6 or 7, wherein the Her-2/neu fusion protein produces the immune response, the composition comprising a vaccine further comprising a physiological buffer.

Laus discloses making a GM-CSF-Her2 fusion protein (the extracellular domain (amino acids 1-652) of Her2 (GenBank) and GM-CSF, see Figure 8); polypeptide antigens such as Her-2 coupled to a dendritic cell-binding proteins such as GM-CSF to stimulate T-cell activation (Col. 5, line 42- Col. 6, line 28); using the polypeptide to induce a cellular (T-cell) activation that is multivalent and substantially higher than using the antigens alone (Col. 9, lines 59-62); targeting malignant tumors expressing Her-2 such as human breast and gynecological cancers (Col. 5, line 64-66, Col. 6, lines 19-27); fusion protein compositions administered directly to an individual as a vaccine, in order to stimulate the individual's cellular immunity pathways in vivo, including induction of a cytolytic T-cell response, a helper T-cell response and antibody response (Col. 11, lines 12-21); and eluting recombinant polypeptides into physiological buffer (Example

1). Also, see the attached copy of the sequence alignment for SEQ ID NOS:6 and 7 with the sequence of Laus.

Applicant is reminded that because the claims recite "comprising" language, any fusion polypeptide comprising an amino acid sequence comprising SEQ ID NO:6 or 7 is encompassed by the claims, and therefore anticipated by Laus.

Conclusion

16. No claims are allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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